CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761377Orig1s000

OTHER REVIEW(S)

MEMORANDUM
LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	July 29, 2025
Requesting Office or Division:	Division of Ophthalmology (DO)
Application Type and Number:	BLA 761377
Product Name, Dosage Form, and Strength:	Eydenzelt (aflibercept-boav) injection, 2 mg/0.05 mL
Applicant Name:	Celltrion, Inc.
FDA Received Date:	April 18, 2025
TTT ID #:	2023-5348-3
DMEPA 1 Safety Evaluator:	Sofanit Getahun, PharmD, BCPS
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

Celltrion, Inc. resubmitted Prescribing Information (PI), Prefilled Syringe (PFS) and Vial container labels, PFS blister and carton labeling, received on April 18, 2025, for Eydenzelt. The Division of Ophthalmology (DO) requested that we review the labels and labeling for Eydenzelt (Appendix A) to determine if they are acceptable from a medication error perspective. The submission is part of Celltrion's response to the Complete Response (CR) letter issued on March 26, 2025[a].

2 REGULATORY HISTORY

Celltrion, Inc. originally submitted BLA 761377 on July 29, 2029, as proposed (b) (4) to the US-licensed Reference Product (RP) Eylea (aflibercept), BLA 125387; which received a CR letter on June 27, 2024[b], due to issues with product quality and facility inspection. Subsequently, Celltrion, Inc. Submitted a Class 2 Resubmission of BLA 761377 on September 26, 2024, which also received a CR letter on March 26, 2025[c], due to issues with facility inspection.

We note that during the previous review cycle our labeling recommendations[d,e] were communicated to the Applicant and the Applicant had implemented some of the recommended revisions[f] at that time.

Thus, Celltrion, Inc. submitted a Class 2 Resubmission of BLA 761377 on April 18, 2025, including the PI, PFS and vial container labels, PFS blister and carton labeling, which are the subject of this review.

3 CONCLUSION

Our evaluation of the proposed Eydenzelt Prescribing Information (PI), Prefilled Syringe (PFS) and Vial container labels, PFS blister and carton labeling did not identify additional areas of vulnerability that may lead to medication errors. We have no recommendations at this time.

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[a] Semiday on behalf of Boyd, W. Complete Response for BLA 761377. Silver Spring (MD): FDA, CDER, OND, Division of Ophthalmology (DO) (US)S; 2025 MAR 26. Available form: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af807a999b

[b] Semiday on behalf of Boyd, W. Complete Response for BLA 761377. Silver Spring (MD): FDA, CDER, OND, Division of Ophthalmology (DO) (US)S; 2024 JUN 27. Available form: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80751f45

[c] Semiday on behalf of Boyd, W. Complete Response for BLA 761377. Silver Spring (MD): FDA, CDER, OND, Division of Ophthalmology (DO) (US)S; 2025 MAR 26. Available form: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af807a999b

[d] Birkemeier, D. Label and Labeling Review for Eydenzelt (BLA 761377). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 DEC 28. TTT ID: 2023-5348.

[e] Getahun, S. Label and Labeling Review for Eydenzelt (BLA 761377). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 DEC 18. TTT ID: 2023-5348-1.

[f] Getahun, S. Memorandum Review of Revised Label and Labeling for Eydenzelt (BLA 761377). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2025 FEB 18. TTT ID: 2023-53482.

APPENDIX A. LABELS AND LABELING

A.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[g] along with postmarket medication error data, we reviewed the following Eydenzelt labels and labeling submitted by Celltrion, Inc..

- Prescribing Information received on April 18, 2025, available from
  - Annotated version: \\CDSESUB1\EVSPROD\bla761377\0047\m1\us\draft-labeling-text-tracked.docx
  - Clean version: \\CDSESUB1\EVSPROD\bla761377\0047\m1\us\draft-labeling-text.docx
- PFS and Vial container labels received on April 18, 2025
- PFS blister and carton labeling received on April 18, 2025

A.2 Container Labels and Carton Labeling Images:

PFS label	Vial label
(b) (4)	(b) (4)

[g] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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VALERIE S VAUGHAN
07/29/2025 11:59:27 AM

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS

INTERCENTER CONSULT MEMORANDUM

Instructions | Submission Information

Date	3/20/2025		
To:	KRISTINE LEAHY		
Requesting Center/Office:	CDER/OPQ	**Clinical Review Division:**	N/A-OPQ/OSE led
From	Gang Peng OPEQ/OHT3/DHT3C		
Through (Team)	Guo Rong, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	Shruti Mistry OPEQ/OHT3/DHT3C		
Subject	ICC2400984 BLA761377		
	Final Recommendation Date: 3/20/2025 ☑ Luer connection performance of the PFS manufactured from the newly added manufacturing site Patheon is comparable to the PFS manufactured from the original site.		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)
GANG PENG -S	Rong Guo -S Digitally signed by Rong Guo -S	

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1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	ICC2400984 BLA761377
Sponsor	Parexel International
Drug/Biologic	EYDENZELT (CT-P42) – proposed biosimilar to Eylea (aflibercept)
Indications for Use	Neovascular (Wet) Age-Related Macular Degeneration (AMD)
Device Constituent	Pre-Filled Syringe
Related Files	ICC2300708-previous CDRH ICCR memo, CDRH had no issues with the device, device performance(luer) and package testing was covered

Review Team	
Lead Device Reviewer	*Gang Peng*

Important Dates	
Final Lead Device Review Memo Due	2/26/2025
BsUFA Resubmission	Mar 26, 2025

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

☑ Approvable – the device constituent of the combination product is approvable for the proposed indication.

☐ Approvable with PMC or PMR, See Section 2.3

☐ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, see Section 2.2.

Section	Adequate			Reviewer Notes
	Yes	No	NA	
Device Description	x			
Labeling	x			
Design Controls	x			
Risk Analysis	x			
Design Verification	x			
Consultant Discipline Reviews			x	
Clinical Validation			x	
Human Factors Validation			x	
Facilities & Quality Systems	x			

2.1. Comments to the Review Team

☑ CDRH does not have any further comments to convey to the review team.

☐ CDRH has the following comments to convey to the review team:

2.2. Complete Response Deficiencies

☑ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.

☐ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

2.3. Recommended Post-Market Commitments/Requirements

CDRH has Post-Market Commitments or Requirements	☐
CDRH does not have Post-Market Commitments or Requirements	☑

TABLE OF CONTENTS

Update Table of Contents

3. PURPOSE/BACKGROUND

3.1. Scope

Parexel is requesting approval of EYDENZELT (CT-P42) – proposed biosimilar to Eylea (aflibercept). The device constituent of the combination product is a Co-Packaged Syringe.

CDER/OPQ has requested the following consult for review of the device constituent of the combination product:

BLA Resubmission after CR, dated 9/26/24. We request CDRH consult depending on how comparable the pre-change and post-change products are, making sure their initial determination for the device component of the combination product still holds.

The goal of this memo is to provide a recommendation of the approvability of the proposed supplement; specifically related to changes that may impact the device constituent of the combination product. The Sponsor is proposing the following change(s) in this supplement:

transitioning the manufacturing of CT-P42 PFS (uDP and aDP) to newly proposed manufacturing sites, Patheon and Steripack

This review will cover the following review areas:

Device performance(luer) and manufacturing of new sites In the original review(prior to the resubmission after CR), CDRH only reviewed the luer of the syringe based on the ICCR agreement. As such, in the resubmission, we will cover review of the luer.

This review will not cover the following review areas:

Non device concerns Device aspects outside of luer performance and those covered in original review

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

Under ICC2300708, previous CDRH ICCR memo, we reviewed device performance(luer) and package testing. The device was recommended approvable by CDRH. However, CDER had CR issues with the submission and had to resubmit. The firm has changed manufacturing sites. The device remains the same.

3.2.1. Related Files

See above, no other submissions

3.3. Indications for Use

Combination Product	Indications for Use
EYDENZELT (CT-P42) – proposed biosimilar to Eylea (aflibercept)	Neovascular (Wet) Age-Related Macular Degeneration (AMD)
Co-Packaged Syringe	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed	
Sequence	**Module(s)**

38	M1
	M3

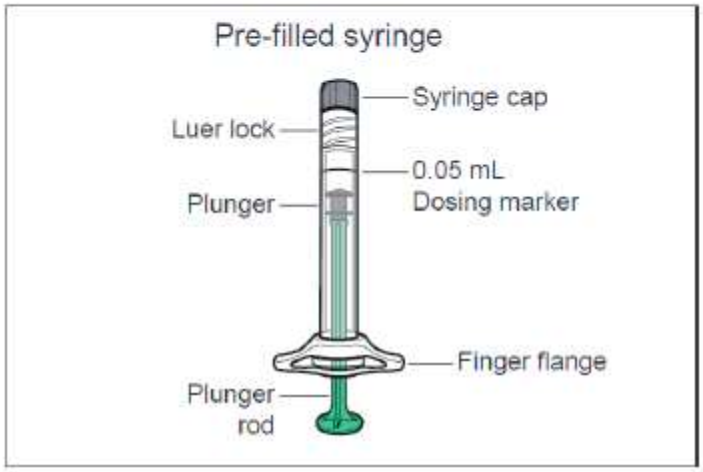
4. DEVICE DESCRIPTION

4.1. Device Description

The CT-P42 drug product is provided as a co-packaged vial kit with filter needle, syringe and injection needle or as a pre-filled syringe (PFS). The CT-P42 vial kit and PFS are intended for intravitreal administration of a single dose of CTP42 solution for injection. The intended user sets the dose by aligning the plunger with the dosing marker shown on the syringe of the vial kit or on the syringe barrel of the CT-P42 PFS.

Vial Kit: A vial of CT-P42 is co-packaged with one 18G filter needle with 5 μm filter, a 1 mL luer-lock plastic syringe and a 30G injection needle to create the vial kit (Figure 3.2.R.10-1)

PRE-FILLED SYRINGE DESCRIPTION – Figure 1:



4.1.1. Specific Changes to the Device Constituent

The device has not changed from the original submission
In response to CR from CDER, the manufacturing site has changed:

Proposed Commercial Manufacturer of CT-P42 PFS Drug Product	
Initial in BLA	**Resubmission of BLA**
(b) (4)	Patheon Italia S.p.A., Via Morolense 5, Ferentino, 03013, Italy [FEI # 3004110157]

Table 3.2.P.3.1-1: CT-P42 PFS Drug Product Manufacturers

Company	Responsibility
CELLTRION, Inc. (Plant (b) (4) (b) (4) Academy-ro, Yeonsu-gu, Incheon, 22014, Republic of Korea	• Release testing of CT-P42 drug product [1] • Stability testing of CT-P42 drug product
CELLTRION, Inc. (Plant (b) (4) (b) (4) Academy-ro 51 beon-gil, Yeonsu-gu, Incheon, 22014, Republic of Korea	• Design controls of CT-P42 drug product • Release testing of CT-P42 drug product [1] • Stability testing of CT-P42 drug product • Holding and storing of CT-P42 finished drug product (fDP)
Patheon Italia S.p.A., Via Morolense 5, Ferentino, 03013, Italy	• Production of CT-P42 drug product • Primary packaging and storage (b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
CELLTRION Pharm, Inc. 82, 2 Sandan-ro, Ochang-eup, Cheongwon-gu, Cheongju-si, Chungcheongbuk-do, 28117, Republic of Korea	• Secondary packaging (cartoning) • Holding and storing of CT-P42 finished drug product (fDP)

[1] Refer to Section 3.2.P.5.3 and Table 3.2.P.3.1-4 for the test items carried out in each testing site.

Table 3.2.P.3.1-2: CT-P42 PFS Device Component Manufacturers

Supplier	Device Component	Quality System
(b) (4)		ISO 13485; 2016
		ISO 13485; 2016
		ISO 13485; 2016
		ISO 13485; 2016

Release Testing Responsibilities(new site has device performance responsibilities)

Table 3.2.P.3.1-4: QC Testing Sites for Lot Release and Stability Tests for CT-P42 PFS Drug Product

Routine Control	Testing Item	CELLTRION Plant (b) (4)	CELLTRION Plant (b) (4)	Patheon, Ferentino	Steripack	Sterigenics Germany GmbH
Release	Appearance (clarity and color)	✓	-	✓	-	-
	Appearance (visible particles)	✓	-	-	-	-
	Sub-visible Particles	✓	-	-	-	-
	Osmolality	✓	-	-	-	-
	pH	✓	-	-	-	-
	Extractable Volume	✓	-	-	-	-
	Break Loose Force and Gliding Force (BLGF)	✓	-	✓	-	-
	Sterility	-	-	✓	-	-
	Endotoxin	-	-	✓	-	
	Sterility of Syringe	-	-	-	-	✓
	Capillary Isoelectric Focusing (cIEF)	✓	-	-	-	-
	Peptide Mapping	✓	-	-	-	-
	Oligosaccharide Profile	✓	-	-	-	-
	CE-SDS (Non-reduced/Reduced)	✓	-	-	-	-
	SEC-HPLC	✓	-	-	-	-
	Isoaspartate Assay	✓	-	-	-	-
	Protein Concentration (UV280)	✓	✓	✓	-	-
	Cell-based hVEGF Blockade Assay	✓	-	-	-	-
	VEGF Binding Affinity (ELISA)	✓	-	-	-	-
	Polysorbate 20	✓	-	-	-	-

Stability Testing Responsibilities(no change, new site has none)

Routine Control	Testing Item	CELLTRION Plant (b) (4)	CELLTRION Plant (b) (4)	Patheon, Ferentino	Steripack	Sterigenics Germany GmbH
Stability	Appearance (clarity, color and visible particles)	✓	-	-	-	-
	Sub-visible Particles	✓	-	-	-	-
	Osmolality	✓	-	-	-	-
	pH	✓	-	-	-	-
	Extractable Volume	✓	-	-	-	-
	Break Loose Force and Gliding Force (BLGF)	✓	-	-	-	-
	Capillary Isoelectric Focusing (cIEF)	✓	-	-	-	-
	CE-SDS (Non-reduced/Reduced)	✓	-	-	-	-
	SEC-HPLC	✓	-	-	-	-
	Isoaspartate Assay	✓	-	-	-	-
	Protein Concentration (UV280)	✓	✓	-	-	-
	Cell-based hVEGF Blockade Assay	✓	-	-	-	-
	VEGF Binding Affinity (ELISA)	✓	-	-	-	-
	Polysorbate 20	✓	-	-	-	-
	Container Closure Integrity Test	-	✓	-	-	-
	Container Closure Integrity Test of Sterile Barrier System	-	-	-	✓	-

- : No Testing

4.2. Steps for Using the Device

See draft labeling text document:

PFS

The carton is opened and the components are removed
Twist of syringe cap
Attach the needle to PFS
Check for bubbles and inject

Vial

Remove packaging
Disinfect top of vial
Assemble syringe and needle
Withdraw the vial contents into the syringe/needle
Ready for injection

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION	
Mid-Cycle Deficiencies: ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The device has not changed, it is a co packaged syringe needle with vial or a PFS presentation. The firm's responses has changed the (b) (4) site to pantheon site. The new pantheon site is responsible for primary packaging and release testing.	

CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No

5. FACILITIES & QUALITY SYSTEMS TRIAGE

5.1. Facilities Inspection Recommendation

Is a new facility or manufacturing process being implemented as a result of this supplement?	☑ Yes ☐ No (No facilities review)

Firm Name:	Patheon Italia S.p.A.,
Address:	Via Morolense 5, Ferentino, 03013, Italy
FEI:	[FEI # 3004110157]
Responsibilities:	See above, includes release testing and primary packaging

Inspectional History
An analysis of the firm's inspection history over the past 2 years:
☑ Inspection was conducted 6/6/2022 to 6/14/2022. The inspection covered drug CGMP and was classified NAI.

☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation:
☐ A post-approval inspection is required because:
The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
A recent medical device inspection of the firm Choose an item.

☑ An inspection is not required because the manufacturing site does not require an inspection at this time given the risk of the combination product.

Add Additional Facility

☐ **No Additional Facilities to Review**

5.2. Quality System Documentation Triage Checklist

The changes proposed impact the quality systems:	☐ Yes ☑ No QS Review is needed **because**: device is PFS and copackaged syringe/needle, based on drug and device risk, QS is not needed, this review, like the previous ICCR, will focus on luer performance

5.3. Facilities & Quality Systems Review Triage Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW RECOMMENDATIONS
Facilities Inspection Recommendation: ☐ (PAI) Pre-Approval Inspection ☐ Post-Approval Inspection ☐ Routine Surveillance ☑ No Inspection ☐ N/A (Select this is a Facilities review is not being conducted) **Site(s) needing inspection:**
Quality System Review Required: ☐ Yes ☐ No ☑ N/A
Reviewer Comments The changes do not necessitate a facilities/QS update.

6. LABELING

☐ The proposed changes involve changes to the labeling of the device constituent and require review (See review below)
☑ The proposed changes do not impact the labeling and therefore the labeling was not reviewed

7. DESIGN CONTROL SUMMARY

In the original documentation, I did not find testing for the luer to demonstrate it will perform as expected. An IR was sent 2/16/25

(b) (4)

Firm Response 2/18/25
CELLTRION would like to clarify that the primary packaging components of CT-P42, (b) (4) (b) (4) 0.5 mL luer lock with ink dose mark (Section 3.2.P.7 [PFS]) remains unchanged despite the change of PFS manufacturing site from (b) (4) to Patheon in BLA resubmission. The syringes and stoppers used for manufacturing CT-P42 PFS at Patheon are supplied as "ready to fill" from (b) (4) (b) (4)
Patheon is limited to (b) (4)
The luer testing results to support the functional performance of the luer in CT-P42 PFS have been requested in the Information Request for BLA 761377 dated April 19, 2024 and CELLTRION duly submitted a response that luer lock syringe for CT-P42 PFS meets the intended functionality per ISO 80369-7 in Response to Information Request of SN0028.

It should be noted that the mentioned ISO 11608 in the Information Request - Needle-based injection systems for medical use - Requirements and test methods (ISO11608-3:2022) refers the compliance with ISO 80369-7 as it governs the luer connections as follows;
"*If any connection uses a Luer connection, the connector shall conform with ISO 80369-7.*"
(b) (4)
(b) (4) Therefore, the luer performance remains compliant with applicable standards, and no additional testing is deemed necessary beyond compliance with ISO 80369-7 requirements that has been demonstrated in previous IR response (Response to Information Request of SN0028). Furthermore, container closure integrity testing (CCIT) for primary packaging of CT-P42 PFS was conducted on the process validation lots (Section 3.2.P.2.5.4 [PFS]) and stability testing is performed per FDA guidance *Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products* (FDA, 2008) (Section 3.2.P.8.1.4 [PFS]). Therefore, there is no risk associated with the drug leakage for the manufactured CT-P42 PFS.

Reviewer Comment
The firm argues that since the new site takes the syringe components from (b) (4) and does not alter them, luer performance will not be affected. The new site is responsible for (b) (4) This process does not have a significant impact on luer performance. With no force being applied directly to the luer, the performance of the luer(for leaking/cracking) should not be significantly different. There are no additional concerns on the luer performance based on the firm's explanation. The change of sites is acceptable.

Add Additional Information Request

☐ **No Additional Information Requests – Finalize Facilities & QS Review Section**

<<END OF REVIEW>>

8. APPENDIX A (INFORMATION REQUESTS)

8.1. Mid-Cycle Information Requests

8.2. Interactive Information Requests

8.2.1. Interactive Information Requests sent on Click or tap to enter a date.

9. APPENDIX B (CONSULTANT MEMOS)

9.1. Human Factors Review Memo – Insert Consultant Name
9.2. Clinical Review Memo – Insert Consultant Name
9.3. Insert Discipline Review Memo – Insert Consultant Name

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: February 25, 2025

To: Dheera Semidey, Senior Regulatory Health Project Manager
Division of Regulatory Operations for Specialty Medicine (DROSM)
Ophthalmology

From: Carrie Newcomer, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for EYDENZELT® (aflibercept-boav) injection, for intravitreal use

BLA: 761377

Background:
In response to DROSM's consult request dated August 23, 2023, OPDP has reviewed the proposed Prescribing Information (PI) and carton and container labeling for the original BLA submission for EYDENZELT® (aflibercept-boav) injection, for intravitreal use.

PI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on February 11, 2025, and we do not have any comments at this time.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on September 26, 2024, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Carrie Newcomer at carrie.newcomer@fda.hhs.gov.

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/s/

CARRIE A NEWCOMER
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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	February 18, 2025
Requesting Office or Division:	Division of Ophthalmology (DO)
Application Type and Number:	BLA 761377
Product Name, Dosage Form, and Strength:	Eydenzelt (aflibercept-boav)injection, 2 mg/0.05 mL
Applicant Name:	Celltrion, Inc.
FDA Received Date:	February 14, 2025
TTT ID #:	2023-5348-2
DMEPA 1 Safety Evaluator:	Sofanit Getahun, PharmD, BCPS
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

Celltrion, Inc. submitted revised prefilled syringe (PFS) container label, blister and carton labeling received on February 14, 2025 for Eydenzelt. The Division of Ophthalmology (DO) requested that we review the revised PFS container label, blister and carton labeling for Eydenzelt (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review,[a] as well as recommendations and requests for clarification from our Office of Therapeutic Biologic and Biosimilars (OTBB) colleagues.

2 CONCLUSION

Celltrion, Inc. implemented all of our recommendations. Additionally, we note that Celltrion proposes to represent the month as "MM" on their revised label and labeling. They included an image of the PFS as part of their information request response,[b] which depicts that the expiration date will be represented using (b) (4).

We have no additional recommendations at this time.

[a] Getahun, S. Label and Labeling Review for Eydenzelt (BLA 761377). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 DEC 18. TTT ID: 2023-5348-1.

[b] Multiple Module Information Amendment (Eydenzelt BLA 761377). Incheon (Republic of Korea): Celltrion, Inc.; 2025 FEB 14. Available from: \\CDSESUB1\EVSPROD\bla761377\0041\m1\us\multiple-information-amendment.pdf

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VALERIE S VAUGHAN
02/18/2025 03:03:51 PM

This is a corrected review that does not change the overall recommendations/conclusions of the original review dated December 18, 2024.

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	December 18, 2024
Requesting Office or Division:	Division of Ophthalmology (DO)
Application Type and Number:	BLA 761377
Product Name, Dosage Form, and Strength:	Eydenzelt (aflibercept-boav)injection, 2 mg/0.05 mL
Product Type:	Combination Product (Drug-Biologic)
Rx or OTC:	Prescription (Rx)
Applicant Name:	Celltrion, Inc.
FDA Received Date:	September 26, 2024
TTT ID #:	2023-5348-1
DMEPA 1 Safety Evaluator:	Sofanit Getahun, PharmD, BCPS
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 INTRODUCTION

As part of the approval process for Eydenzelt (aflibercept-boav) injection, the Division of Ophthalmology (DO) requested that we review the proposed Eydenzelt Prescribing Information (PI), vial and prefilled syringe (PFS) container labels and carton labeling, as well as PFS blister tray for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

Eydenzelt (aflibercept-boav) is a proposed [redacted] (b) (4) to the US-licensed Reference Product (RP) is Eylea (aflibercept), BLA 125387.

1.2 REGULATORY HISTORY

Celltrion, Inc. previously submitted BLA 761377 on July 29, 2023, which received a Complete Response letter on June 27, 2024, due to issues with product quality and facility inspection.[a]

Thus, Celltrion, Inc. submitted a Class 2 Resubmission of BLA 761377 on September 26, 2024.[b]

2 MATERIALS REVIEWED

This section lists the materials considered for our review of BLA 761377.

Table 1. Materials Considered for this Label and Labeling Review	
Material(s) Reviewed	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Previous DMEPA Reviews	C

3 CONCLUSION

We evaluated the proposed Eydenzelt Prescribing Information (PI) and determined that it is acceptable from a medication error perspective.

However, the proposed Eydenzelt PFS label and PFS blister labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for Celltrion, Inc. in Section 4.

[a] Semiday on behalf of Boyd, W. Complete Response for BLA 761377. Silver Spring (MD): FDA, CDER, OND, Division of Ophthalmology (DO) (US); 2024 JUN 27.
[b] Cover Letter (Eydenzelt BLA 761377). Incheon (Republic of Korea): Celltrion, Inc.; 2024 SEP 26. Available from: \\CDSESUB1\EVSPROD\bla761377\0038\m1\us\cover-letter.pdf

4 RECOMMENDATIONS FOR CELLTRION, INC.

Table 2. Identified Issues and Recommendations for Celltrion, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
PFS Label			
1.	As currently presented, the dosage form "*injection*" is not included on the principal display panel (PDP).	The dosage form is considered to be "critical information" that should appear on the PDP to *"allow for proper identification of the product."* For more information see Guidance for industry *"Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.*[c]*"*	Add the dosage form "*injection*" on the PDP. To ensure sufficient space, we recommend removing the statement "(b) (4) " from the PDP of the syringe label.
PFS Blister Labeling			
1.	The linear barcode is missing.	The drug barcode is often used as an additional verification during the medication use process; therefore, it is an important safety feature that should be part of the label and is a requirement per 21 CFR 201.25 (C)(2).	Add the linear barcode to the PFS blister labeling in accordance with 21 CFR 201.25 (C)(2). The barcode should be placed in a conspicuous location where it will not be difficult to read because of distorted text, and in an area where it will not be damaged because it appears at the point of label separation (e.g., perforation).

[c] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. May 2022. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors.

APPENDICES: METHODS AND RESULTS FOR EACH MATERIALS REVIEWED

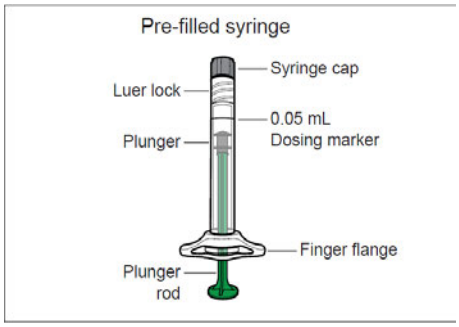
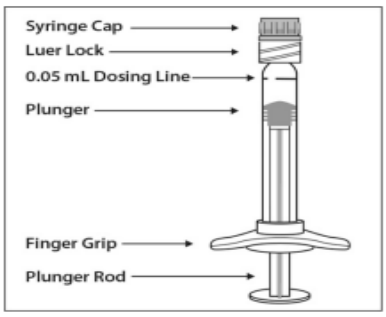
APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 3 presents relevant product information for Eydenzelt received on September 26, 2024 from Celltrion, Inc., and the US-licensed Reference Product (RP).

Table 3. Relevant Product Information for Eydenzelt and the US-licensed Reference Product (RP).		
Product Name	Eydenzelt	Eylea[d] (BLA 125387)
Initial Approval Date	N/A	November 18, 2011
Active Ingredient	aflibercept-boav	aflibercept
Indication	• Neovascular (Wet) Age-related Macular Degeneration (AMD) • Macular Edema Following Retinal Vein Occlusion (RVO) • Diabetic Macular Edema (DME) • Diabetic Retinopathy (DR)	• Neovascular (Wet) Age-related Macular Degeneration (AMD) • Macular Edema Following Retinal Vein Occlusion (RVO) • Diabetic Macular Edema (DME) • Diabetic Retinopathy (DR) • Retinopathy of Prematurity (ROP)
Dosage Form	injection	
Strength	2 mg/0.05 mL	
Route of Administration	Intravitreal injection	

[d] Eylea [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. October 2024. [cited 2024 NOV 01]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125387s087lbl.pdf

Table 3. Relevant Product Information for Eydenzelt and the US-licensed Reference Product (RP).		
Product Name	Eydenzelt	Eylea[d] (BLA 125387)
Dose and Frequency	Neovascular (Wet) Age-related Macular Degeneration (AMD): 2 mg administered by intravitreal injection every 4 weeks for the first 12 weeks, followed by 2 mg via intravitreal injection once every 8 weeks. Although Eydenzelt may be dosed as frequently as 2 mg every 4 weeks, additional efficacy was not demonstrated in most patients when aflibercept was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week dosing after the first 12 weeks. Although not as effective as the recommended every 8 week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy. Macular Edema Following Retinal Vein Occlusion (RVO): 2 mg administered by intravitreal injection once every 4 weeks. Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR): 2 mg administered by intravitreal injection every 4 weeks for the first 5 injections, followed by 2 mg via intravitreal injection once every 8 weeks. Although Eydenzelt may be dosed as frequently as 2 mg every 4 weeks, additional efficacy was not demonstrated in most patients when aflibercept was dosed every	Neovascular (Wet) Age-related Macular Degeneration (AMD): 2 mg administered by intravitreal injection every 4 weeks for the first 12 weeks, followed by 2 mg via intravitreal injection once every 8 weeks. Although Eylea may be dosed as frequently as 2 mg every 4 weeks, additional efficacy was not demonstrated in most patients when aflibercept was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week dosing after the first 12 weeks. Although not as effective as the recommended every 8 week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy. Macular Edema Following Retinal Vein Occlusion (RVO): 2 mg administered by intravitreal injection once every 4 weeks. Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR): 2 mg administered by intravitreal injection every 4 weeks for the first 5 injections, followed by 2 mg via intravitreal injection once every 8 weeks. Although Eylea may be dosed as frequently as 2 mg every 4 weeks, additional efficacy was not demonstrated in most patients when aflibercept was dosed every 4 weeks

Table 3. Relevant Product Information for Eydenzelt and the US-licensed Reference Product (RP).		
Product Name	Eydenzelt	Eylea[d] (BLA 125387)
	4 weeks compared to every 8 weeks. Some patients may need every 4 week dosing after the first (b) (4) weeks.	compared to every 8 weeks. Some patients may need every 4 week dosing after the first (b) (4) weeks. <u>Retinopathy of Prematurity (ROP):</u> 0.4 mg administered by intravitreal injection. Treatment is initiated with a single injection per eligible eye and may be given bilaterally on the same day. Injections may be repeated in each eye. The treatment interval between doses injected into the same eye should be at least 10 days.
How Supplied	Prefilled syringe Vial Kit with Injection Components	
Storage	2°C to 8ºC (36°F to 46ºF). Do not freeze. Do not use beyond the date stamped on the carton and container label. Store in the original carton until time of use to protect from light. Do not open sealed blister tray until time of use.	
Container Closure		

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error data, we reviewed the following Eydenzelt labels and labeling submitted by Celltrion, Inc..

- Prescribing Information received on September 26, 2024, available from \\CDSESUB1\EVSPROD\bla761377\0038\m1\us\draft-labeling-text.docx
- Container label(s) received on September 26, 2024
- Carton labeling received on September 26, 2024
- Prefilled Syringe Blister labeling received on September 26, 2024

B.2 Container Labels and PFS Blister and Carton Labeling Images

Container labels

Prefilled Syringe (PFS) Label	Vial Label
(b) (4)	(b) (4)

[e] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

APPENDIX C. PREVIOUS DMEPA REVIEWS

On October 21, 2024, we searched for previous DMEPA reviews relevant to this current review using the terms, aflibercept, Eydenzelt, and BLA 761377. Our search identified fourteen (14) previous reviews since the date of our last search on July 27, 2023, and we considered our previous recommendations to see if they are applicable for this current review.

Table 4. List of Previous DMEPA Reviews for aflibercept

Application #	Product name	Applicant	Strength	Status	Previous DMEPA Reviews
BLA 125387/S-080	Eylea (aflibercept) injection	Regeneron	2 mg/0.05 mL	Approved 08/31/2023	2023-5499[f]
BLA 761274	Yesafili (aflibercept-jbvf)	Biocon Biologics, Inc.	2 mg/0.05 mL	Approved 05/20/2024	2022-582-1[g] 2022-582-2[h]
BLA 761350	Opuviz (aflibercept-yszy)	Samsung Bioepis	2 mg/0.05 mL	Approved 05/20/2024	2023-3737-1[i]
BLA 761378	Ahzantive (aflibercept-mrbb)	Formycon AG	2 mg/0.05 mL	Approved 06/28/2024	2023-5353[j] 2023-5353-1[k]
BLA 761382	Enzeevu (aflibercept-abzv)	Sandoz Inc.	2 mg/0.05 mL	Approved 08/09/2024	2023-5922[l] 2023-5922-1[m] 2023-5922-2[n]

[f] Getahun, S. Memorandum Review of Revised Label and Labeling for Eylea (BLA 125387/S-080). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 AUG 11. TTT ID No.: 2023-5499.

[g] Myers, D. Memorandum Review of Revised Label and Labeling for Yesafili (BLA 761274). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 MAR 01. TTT ID No.: 2022-582-1.

[h] Myers, D. Memorandum Review of Revised Label and Labeling for Yesafili (BLA 761274). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 APR 12. TTT ID No.: 2022-582-2.

[i] Getahun, S. Memorandum Review of Revised Label and Labeling for Opuviz (BLA 761350). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 FEB 06. TTT ID No.: 2023-3737-1.

[j] Getahun, S. Label and Labeling Review for FYB203 (aflibercept-xxxx) (BLA 761378). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 DEC 12. TTT ID No.: 2023-5353

[k] Getahun, S. Memorandum Review of Revised Label and Labeling for Ahzantive (BLA 761378). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 JUN 03. TTT ID No.: 2023-5353-1

[l] Getahun, S. Label and Labeling Review for SOK583 (aflibercept-xxxx) (BLA 761382). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 JAN 19. TTT ID No.: 2023-5922.

[m] Getahun, S. Memorandum Review of Revised Label and Labeling for Enzeevu (BLA 761382). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 JUN 03. TTT ID No.: 2023-5922-1.

[n] Getahun, S. Memorandum Review of Revised Label and Labeling for Enzeevu (BLA 761382). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 AUG 01. TTT ID No.: 2023-5922-2.

BLA 761298	Pavblu (aflibercept-ayyh)	Amgen Inc.	2 mg/0.05 mL	Approved 08/23/2024	2023-6174[o] 2023-6174-1[p] 2023-6174-2[q]
[redacted] (b) (4)					
BLA 761377	Eydenzelt (aflibercept-boav)	Celltrion, Inc.	2 mg/0.05 mL	Complete Response 06/27/2024	2023-5348[s]
BLA 761377	Eydenzelt (aflibercept-boav) injection	Celltrion, Inc.	2 mg/0.05 mL	Subject of this review	2023-5348-1

[o] Getahun, S. Label and Labeling Review for Pavblu (BLA 761298). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 MAR 08. TTT ID No.: 2023-6174.

[p] Getahun, S. Memorandum Review of Revised Label and Labeling for Pavblu (BLA 761298). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 MAY 14. TTT ID No.: 2023-6174-1.

[q] Getahun, S. Memorandum Review of Revised Label and Labeling for Pavblu (BLA 761298). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 JUL 25. TTT ID No.: 2023-6174-2.

[redacted] (b) (4)

[s] Birkemeier, D. Label and Labeling Review for Eydenzelt (BLA 761377). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 DEC 28. TTT ID No.: 2023-5348.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SOFANIT N GETAHUN
02/14/2025 10:28:21 AM

VALERIE S VAUGHAN
02/14/2025 10:39:22 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	December 28, 2023
Requesting Office or Division:	Division of Ophthalmology (DO)
Application Type and Number:	BLA 761377
Product Name, Dosage Form, and Strength:	Eydenzelt (aflibercept-xxxx[a]) injection, 2 mg/0.05 mL
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Celltrion Inc. (Celltrion)
FDA Received Date:	June 29, 2023
TTT ID #:	2023-5348
DMEPA 1 Safety Evaluator:	Damon Birkemeier, PharmD, FISMP, NREMT
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

[a] The non-proprietary name suffix for this product has not yet been determined; therefore, the placeholder aflibercept-xxxx is used throughout this review to refer to the non-proprietary name and suffix for this product.

1. REASON FOR REVIEW

As part of the approval process for Eydenzelt (aflibercept-xxxx) injection, the Division of Ophthalmology (DO) requested that we review the proposed Eydenzelt prescribing information, container labels, prefilled syringe (PFS) blister tray labeling, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

BLA 761377 is a proposed [redacted] (b) (4) biosimilar to US-licensed Eylea (hereafter called Eylea) (BLA 125387).

2. MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3. CONCLUSIONS AND RECOMMENDATIONS

The proposed prescribing information, container labels, PFS blister tray labeling, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Celltrion Inc.

Note that DMEPA 1 is evaluating the human factors comparative analysis under separate cover and based on the outcome of that review additional label and labeling comments may be forthcoming.

4. RECOMMENDATIONS FOR THE DIVISION OF OPHTHALMOLOGY (DO)

Table 2. Identified Issues and Recommendations for Division of Ophthalmology (DO)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Full Prescribing Information – Section 2 Dosage and Administration			
1.	In subsection 2.3 Preparation for Administration – Vial, we note the product's investigational name "CT-P42" is included.	The proposed proprietary name "Eyedenzelt" was found conditionally acceptable on September 5, 2023.	Remove all instances of the product's investigational name "CT-P42". Replace with the conditionally acceptable name "Eyedenzelt" or proper name, where appropriate.
2.	We note dosages are described using multiple units of measurement.	Concurrent use of multiple units of measurement (i.e., mg, mL, and microliters) increases the risk of confusion and could lead to medication dosing errors.[b]	We recommend revising the dosing recommendations to remove dosage described in terms of mL and microliters. For example, revise to: "The recommended dose for Eyedenzelt is 2 mg administered via intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 12 weeks (3 months), followed by 2 mg via intravitreal injection once every 8 weeks (2 months)."
3.	In subsection 2.2 Preparation for Administration – Pre-filled syringe, we note the statement "The EYDENZELT pre-filled plastic syringe is sterile (b) (4)	We note per Celltrion's submission, "*Of note, ROP indication will not be proposed for licensure of CT-P42 due to orphan drug exclusivity.*"	We recommend removing the statement (b) (4) (b) (4)

[b] Guidance for Industry: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.* 2022. Available from https://www.fda.gov/media/158522/download.

Table 2. Identified Issues and Recommendations for Division of Ophthalmology (DO)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(b) (4)		
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	As currently presented, the appropriate information to facilitate identification of the dosage form is not included.	Section 16 *How Supplied/Storage and Handling* should contain information suitable for product identification in accordance with 21 CFR 201.57(c)(17)(iii).	We recommend including identifying information in Section 16 *How Supplied/Storage and Handling* (e.g., Eydenzelt is a clear to slightly opalescent, colorless to very pale brownish-yellow solution).

5. RECOMMENDATIONS FOR CELLTRION INC.

Table 3. Identified Issues and Recommendations for Celltrion Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	The format for expiration date is not defined.	A clearly defined expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if

Table 3. Identified Issues and Recommendations for Celltrion Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a forward slash be used to separate the portions of the expiration date.
2.	Each numeric value presented in the storage statement is not immediately followed by its intended unit of measurement (i.e., °C or °F).	The presentation of the storage statement should be clearly stated to avoid errors.	Revise the storage statement to read "Store refrigerated at 2°C to 8°C (36°F to 46°F)."
3.	For the carton labeling, vial container label, and PFS blister tray labeling, the terminology within the statement of dosage [(i.e., (b) (4) is inconsistent with the terminology in the Prescribing Information.	To ensure consistency with the terminology in the Prescribing Information.	We recommend revising the statement of dosage to read, (b) (4) Prescribing Information." Additionally, we recommend revising (b) (4) in the (b) (4) statement to "Prescribing Information."
4.	For the vial container label and carton labeling, as currently presented, the packaging type term is listed as "single-use".	The packaging type term is incorrect. Per USP <659> *Packaging and Storage Requirements*, the correct terminology for your product is "single-dose".	Revise the packaging type term to read "single-dose".
Container Labels			
1.	The dosage form (injection) is missing from the vial container label.	The dosage form (injection) should be included on the vial container label.	We recommend including the dosage form (injection) on the vial container label, for example: Eydenzelt (aflibercept-xxxx)

Table 3. Identified Issues and Recommendations for Celltrion Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
			Injection
Carton Labeling			
1.	The phrase "Each single-dose glass vial [pre-filled syringe] is designed to deliver 2 mg of aflibercept-xxxx in 0.05 mL (b) (4) of solution…" statement includes two units of measurement.	We note (b) (4) is not a common terminology of measurement on syringes, and the syringe provided in the kit measures in "mL".	We recommend removing the reference to (b) (4) from this statement.
2.	Under the vial carton contents section, the statement, (b) (4) (b) (4)	(b) (4)	Remove (b) (4) (b) (4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

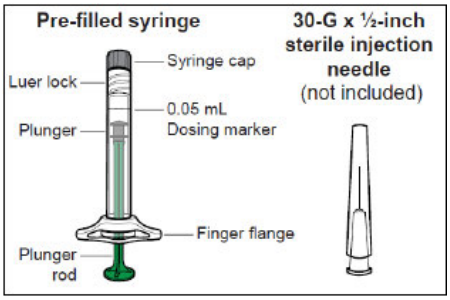
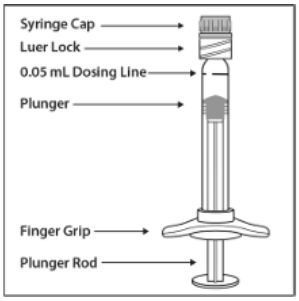
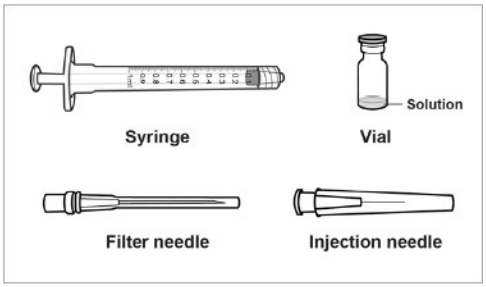
APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table presents relevant product information for Eydenzelt that Celltrion Inc. submitted on June 29, 2023, and Eylea.

Table 4. Relevant Product Information for Listed Drug and Eydenzelt		
Product Name	Eylea	Eydenzelt
Application Type and #	BLA 125387	BLA 761377
Initial Approval Date	November 18, 2011	n/a
Active Ingredient	aflibercept	aflibercept-xxxx
Indication	• Neovascular (Wet) Age-related Macular Degeneration (AMD) • Macular Edema Following Retinal Vein Occlusion (RVO) • Diabetic Macular Edema (DME) • Diabetic Retinopathy (DR) • Retinopathy of Prematurity (ROP)	• Neovascular (Wet) Age-related Macular Degeneration (AMD) • Macular Edema Following Retinal Vein Occlusion (RVO) • Diabetic Macular Edema (DME) • Diabetic Retinopathy (DR)
Route of Administration	Intravitreal	
Dosage Form	Injection	
Strength	2 mg/0.05 mL	
Dose and Frequency	• Neovascular (Wet) Age-related Macular Degeneration (AMD): 2 mg administered by intravitreal injection every 4 weeks for the first 12 weeks, followed by 2 mg via intravitreal injection once every 8 weeks. Although Eylea may be dosed as frequently as 2 mg every 4 weeks, additional efficacy was not demonstrated in most patients when aflibercept was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week dosing after the	• Neovascular (Wet) Age-related Macular Degeneration (AMD): 2 mg administered by intravitreal injection every 4 weeks for the first 12 weeks, followed by 2 mg via intravitreal injection once every 8 weeks. Although Eydenzelt may be dosed as frequently as 2 mg every 4 weeks, additional efficacy was not demonstrated in most patients when aflibercept was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week dosing

	first 12 weeks. Although not as effective as the recommended every 8 week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy. • Macular Edema Following Retinal Vein Occlusion (RVO): 2 mg administered by intravitreal injection once every 4 weeks. Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR): 2 mg administered by intravitreal injection every 4 weeks for the first 5 injections, followed by 2 mg via intravitreal injection once every 8 weeks. Although Eylea may be dosed as frequently as 2 mg every 4 weeks, additional efficacy was not demonstrated in most patients when aflibercept was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week dosing after the first (b) (4) weeks. • Retinopathy of Prematurity (ROP): 0.4 mg administered by intravitreal injection. Treatment is initiated with a single injection per eligible eye and may be given bilaterally on the same day. Injections may be repeated in each eye. The treatment interval between doses injected into the same eye should be at least 10 days.	after the first 12 weeks. Although not as effective as the recommended every 8 week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy. • Macular Edema Following Retinal Vein Occlusion (RVO): 2 mg administered by intravitreal injection once every 4 weeks. • Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR): 2 mg administered by intravitreal injection every 4 weeks for the first 5 injections, followed by 2 mg via intravitreal injection once every 8 weeks. Although Eydenzelt may be dosed as frequently as 2 mg every 4 weeks, additional efficacy was not demonstrated in most patients when aflibercept was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week dosing after the first (b) (4) weeks.

<table>
<tr><td>How Supplied</td><td>
Each prefilled syringe or vial is for single eye use only supplied in the following presentations:
<table>
<tr><th>NDC Number</th><th>Carton Type</th><th>Carton Contents</th></tr>
<tr><td>61755-005-01</td><td>Prefilled syringe</td><td>One blister pack containing one Eylea 2 mg/0.05 mL sterile, single-dose prefilled plastic syringe
One package insert</td></tr>
<tr><td>61755-005-02</td><td>Vial kit with injection components</td><td>One Eylea 2 mg/0.05 mL single-dose glass vial
One 18-gauge x 1½-inch, 5-micron filter needle for withdrawal of vial contents
One 30-gauge x ½-inch injection needle for intravitreal injection
One 1-mL syringe for administration
One package insert</td></tr>
</table>
Each prefilled syringe or vial is for single eye use only supplied in the following presentations:
<table>
<tr><th>NDC Number</th><th>Carton Type</th><th>Carton Contents</th></tr>
<tr><td>72606-026-01</td><td>Prefilled syringe</td><td>One blister pack containing one CT-P42 2 mg/0.05 mL sterile, single-dose prefilled plastic syringe
One package insert</td></tr>
<tr><td>72606-026-02</td><td>Vial kit with injection components</td><td>One CT-P42 2 mg/0.05 mL single-dose glass vial
One 18-gauge x 1½-inch, 5-micron filter needle for withdrawal of vial contents
One 30-gauge x ½-inch injection needle for intravitreal injection
One 1-mL syringe for administration
One package insert</td></tr>
</table>
</td></tr>
<tr><td>Storage</td><td>Refrigerate at 2°C to 8°C (36°F to 46°F). Do not freeze. Do not use beyond the date stamped on the carton and container label. Store in the original carton until time of use to protect from light. Do not open sealed sterilized blister pack until time of use.</td></tr>
</table>

<table>
<tr><td rowspan="4">Container Closure</td><td>Figure 1: CT-P42 PFS</td><td>Figure 2: Eylea PFS</td></tr>
<tr><td> 
</td><td> 
</td></tr>
<tr><td>Figure 3: CT-P42 Vial Kit</td><td>Figure 4: Eylea Vial Kit</td></tr>
<tr><td> 
</td><td>No image in Eylea IFU but the components are the same as Eydenzelt</td></tr>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On July 27, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms aflibercept, Eydenzelt, and BLA 761377. Our search identified ten previous reviews[c,d,e,f,g,h,i,j,k,l] and we considered our previous recommendations to see if they are applicable for this current review.

[c] Fava W. Label and Labeling Review for Eylea (BLA 125387). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2011 AUG 5. OSE RCM No.: 2011-539.

[d] Roosta N. Label and Labeling Review for Eylea (BLA 125387/S-061). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 DEC 27. OSE RCM No.: 2018-2596.

[e] Clark C. Label and Labeling Review for Yesafili (BLA 761274). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 APR 21. OSE RCM No.: 2021-2131.

[f] Getahun S. Label and Labeling Review for Eylea (BLA 125387/S-073). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 JUL 11. OSE RCM No.: 2022-859.

[g] Getahun S. Label and Labeling Review for Eylea (BLA 125387/S-075). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 DEC 19. TTT ID No.: 2022-866.

[h] Birkemeier D. Label and Labeling Review for aflibercept-xxxx (BLA 761355). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 MAR 29. TTT ID No.: 2023-3257.

[i] Birkemeier D. Label and Labeling Review Memo for Eylea HD (BLA 761355). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 JUN 12. TTT ID No.: 2023-3257-1.

[j] Getahun S. Label and Labeling Review for Opuviz (BLA 761350). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 JUL 17. TTT ID No.: 2023-3737.

[k] Getahun S. Label and Labeling Review Memo for Eylea (BLA 125387/S-080). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 AUG 11. TTT ID No.: 2023-5499.

[l] Myers D. Label and Labeling Review Memo for Yesafili (BLA 761274). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 AUG 18. TTT ID No.: 2022-582.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[m] along with postmarket medication error data, we reviewed the following EydenzeIt labels and labeling submitted by Celltrion Inc. received on June 29, 2023.

- Container labels
- Carton labeling
- Blister tray labeling
- Prescribing Information (Image not shown) available from \\CDSESUB1\EVSPROD\bla761377\0001\m1\us\annotated-draft-labeling-text.pdf

[m] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DAMON A BIRKEMEIER
12/28/2023 05:09:48 PM

VALERIE S VAUGHAN
01/02/2024 09:52:44 AM

USE-RELATED RISK ANALYSIS AND COMPARATIVE ANALYSES REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	August 24, 2023
Requesting Office or Division:	Division of Ophthalmology (DO)
Application Type and Number:	BLA 761377
Product Name, Dosage Form, and Strength:	CT-P42[a] (aflibercept-xxxx)[b] injection, 2 mg/0.05 mL
Device Constituent:	Prefilled syringe (PFS) and Vial Kit
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Celltrion Inc. (Celltrion)
FDA Received Date:	June 29, 2023
OSE TTT #:	2023-5344
DMEPA 1 Safety Evaluator:	Damon Birkemeier, PharmD, FISMP, NREMT
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Deputy Director:	Jason Flint, MBA, PMP

[a] CT-P42 has been developed as a proposed (b) (4) biosimilar to US-licensed Eylea (aflibercept) (hereafter called Eylea). At the time this review was written, a proprietary name has not yet been approved, and the proprietary name placeholder, CT-P42, is used throughout the review.

[b] CT-P42 has been developed as a proposed (b) (4) biosimilar to Eylea (aflibercept). At the time this review was written, a non-proprietary name suffix has not yet been approved, and the non-proprietary name placeholder, aflibercept-xxxx, is used throughout the review.

1 REASON FOR REVIEW

This review evaluates the use-related risk analyses (URRA), comparative analyses, and justification for not submitting human factors (HF) data submitted under BLA 761377 for CT-P42 injection 2 mg/0.05 mL prefilled syringe (PFS) and vial kit to determine whether Celltrion needs to submit the results of a comparative use HF validation study to support their marketing application.

Table 1. Relevant Product Information for Proposed Product (CT-P42) and Comparator Product (Eylea)		
	Proposed Product	Comparator Product[c]
Product Name	CT-P42	Eylea
Application #	BLA 761377	BLA 125387
Sponsor/Applicant	Celltrion Inc.	Regeneron Pharmaceuticals, Inc.
Initial Approval Date	N/A	November 18, 2011
Therapeutic Drug Class or New Drug Class	Vascular endothelial growth factor (VEGF) inhibitor	
Active Ingredient	aflibercept-xxxx	aflibercept
Indication	• Neovascular (Wet) Age-related Macular Degeneration (AMD) • Macular Edema Following Retinal Vein Occlusion (RVO) • Diabetic Macular Edema (DME) • Diabetic Retinopathy (DR)	• Neovascular (Wet) Age-related Macular Degeneration (AMD) • Macular Edema Following Retinal Vein Occlusion (RVO) • Diabetic Macular Edema (DME) • Diabetic Retinopathy (DR) • Retinopathy of Prematurity (ROP)
Route of Administration	Intravitreal	
Dosage Form	Injection	
Strength	2 mg/0.05 mL	
Dose and Frequency	• Neovascular (Wet) Age-related Macular Degeneration (AMD): 2 mg administered	• Neovascular (Wet) Age-related Macular Degeneration (AMD): 2 mg administered

[c] Eylea [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. May 2023. [cited July 25, 2023]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/125387s075lbl.pdf.

	by intravitreal injection every 4 weeks for the first 12 weeks, followed by 2 mg via intravitreal injection once every 8 weeks. Although CT-P42 may be dosed as frequently as 2 mg every 4 weeks, additional efficacy was not demonstrated in most patients when aflibercept was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4-week dosing after the first 12 weeks. Although not as effective as the recommended every 8-week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy. • Macular Edema Following Retinal Vein Occlusion (RVO): 2 mg administered by intravitreal injection once every 4 weeks. • Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR): 2 mg administered by intravitreal injection every 4 weeks for the first 5 injections, followed by 2 mg via intravitreal injection once every 8 weeks. Although CT-P42 may be dosed as frequently as 2 mg every 4 weeks, additional efficacy was not demonstrated in most patients when aflibercept was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4-week dosing after the first (b) (4) weeks.	by intravitreal injection every 4 weeks for the first 12 weeks, followed by 2 mg via intravitreal injection once every 8 weeks. Although Eylea may be dosed as frequently as 2 mg every 4 weeks, additional efficacy was not demonstrated in most patients when aflibercept was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4-week dosing after the first 12 weeks. Although not as effective as the recommended every 8-week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy. • Macular Edema Following Retinal Vein Occlusion (RVO): 2 mg administered by intravitreal injection once every 4 weeks. • Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR): 2 mg administered by intravitreal injection every 4 weeks for the first 5 injections, followed by 2 mg via intravitreal injection once every 8 weeks. Although Eylea may be dosed as frequently as 2 mg every 4 weeks, additional efficacy was not demonstrated in most patients when aflibercept was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4-week dosing after the first (b) (4) weeks.

<table>
<tr><td></td><td></td><td>• <u>Retinopathy of Prematurity (ROP):</u> 0.4 mg administered by intravitreal injection. Treatment is initiated with a single injection per eligible eye and may be given bilaterally on the same day. Injections may be repeated in each eye. The treatment interval between doses injected into the same eye should be at least 10 days.</td></tr>
<tr><td>How Supplied</td><td>• Each prefilled syringe or vial is for single eye use only supplied in the following presentations:
<table>
<tr><th>NDC Number</th><th>Carton Type</th><th>Carton Contents</th></tr>
<tr><td>72606-026-01</td><td>Prefilled syringe</td><td>One blister pack containing one CT-P42 2 mg/0.05 mL sterile, single-dose prefilled plastic syringe
One package insert</td></tr>
<tr><td>72606-026-02</td><td>Vial kit with injection components</td><td>One CT-P42 2 mg/0.05 mL single-dose glass vial
One 18-gauge x 1½-inch, 5-micron filter needle for withdrawal of vial contents
One 30-gauge x ½-inch injection needle for intravitreal injection
One 1-mL syringe for administration
One package insert</td></tr>
</table></td><td>• Each prefilled syringe or vial is for single eye use only supplied in the following presentations:
<table>
<tr><th>NDC Number</th><th>Carton Type</th><th>Carton Contents</th></tr>
<tr><td>61755-005-01</td><td>Prefilled syringe</td><td>One blister pack containing one Eylea 2 mg/0.05 mL sterile, single-dose prefilled plastic syringe
One package insert</td></tr>
<tr><td>61755-005-02</td><td>Vial kit with injection components</td><td>One Eylea 2 mg/0.05 mL single-dose glass vial
One 18-gauge x 1½-inch, 5-micron filter needle for withdrawal of vial contents
One 30-gauge x ½-inch injection needle for intravitreal injection
One 1-mL syringe for administration
One package insert</td></tr>
</table></td></tr>
</table>

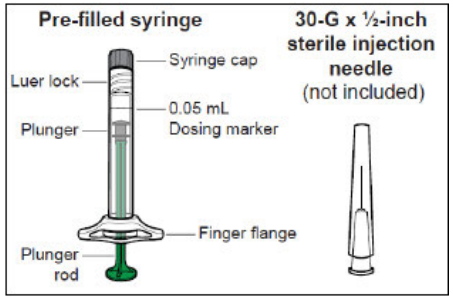
<table>
<tr><td>Storage</td><td colspan="2">Refrigerate at 2°C to 8°C (36°F to 46°F). Do not freeze. Do not use beyond the date stamped on the carton and container label. Store in the original carton until time of use to protect from light. Do not open sealed sterilized blister pack until time of use.</td></tr>
<tr><td>Container Closure/Device Constituent</td><td>Figure 1: CT-P42 PFS
 

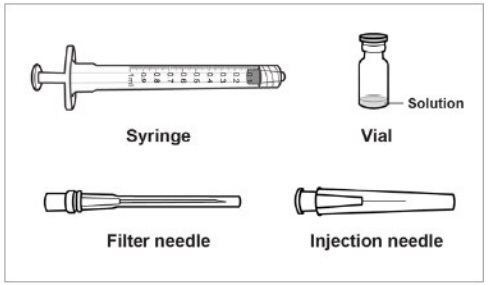
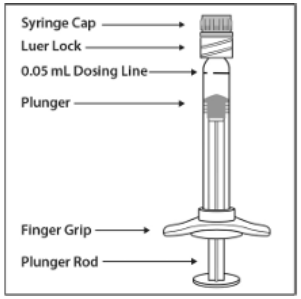
Figure 3: CT-P42 Vial Kit
 
</td><td>Figure 2: Eylea PFS
 

Figure 4: Eylea Vial Kit
No image in Eylea IFU but the components are the same as CT-P42</td></tr>
<tr><td>Intended Users</td><td colspan="2">Qualified ophthalmologists or healthcare professionals (HCPs)</td></tr>
<tr><td>Intended Use Environment</td><td colspan="2">Operating room/theatre or an outpatient clinic</td></tr>
</table>

1.1 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

- On April 29, 2022, Celltrion submitted a Biosimilar Biologic Product Development (BPD) Type 2 Meeting Request for CT-P42 under IND 147335. Specifically, Celltrion submitted the following documents:
    1. CT-P42 PFS Use Related Risk Analysis (URRA)
    2. Comparative Analyses between CT-P42 PFS and Eylea PFS
    3. Comparative Analyses between CT-P42 vial kit and Eylea Vial Kit and justification for not submitting an HF validation study

  Additionally, Celltrion included the following human factors questions:
    1. *Does the Agency agree that the CT-P42 vial kit is classified as a co-package combination product and agree with the proposed human factor study strategy?*
    2. *Does the Agency agree that the CT-P42 Prefilled Syringe (PFS) is classified as a prefilled biologic delivery combination product and agree with the proposed human factor study strategy?*

  On August 11, 2022, we provided a response to Celltrion via a meeting preliminary comments letter. We stated that Celltrion's proposed vial kit and prefilled syringe are combination products. Additionally, we noted that Celltrion's approach to submit a use-related risk analysis (URRA), comparative risk assessment, and justification for not submitting an HF validation study for their proposed CT-P42 PFS and vial kit appears reasonable. We recommended Celltrion submit their comprehensive URRA, comparative risk assessment, and justification for not submitting an HF validation study to the IND for Agency review.[d]
- On October 18, 2022, Celltrion submitted the following documents under IND 147335:
    1. Comparative Analyses between CT-P42 vial kit and Eylea vial kit
    2. HF validation study protocol for the CT-P42 PFS
- On January 19, 2023, we issued a HF validation study protocol – incomplete letter notifying Celltrion that their HF validation study protocol submission (dated October 18, 2022) for their CT-P42 PFS was incomplete as it did not contain a comprehensive URRA. We requested Celltrion submit a new HF validation study protocol that includes all information as detailed in the draft *guidance for industry Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications*. Additionally, based on potential similarities between CT-P42 PFS and Eylea PFS, we notified

[d] Smith J. Meeting Preliminary Comments for CT-P42 (IND 147335). Silver Spring (MD): FDA, CDER, OND, DO (US); 2022 AUG 11. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8067bcda.

Celltrion to consider conducting comparative analyses such as a labeling comparison, a comparative task analysis, and a physical comparison between their proposed product and the Eylea PFS.[e]

- On February 1, 2023, Celltrion resubmitted their HF validation study protocol for their proposed CT-P42 PFS under IND 147335 for Agency review.
- On March 16, 2023, we reviewed the comparative analyses between CT-P42 vial kit and Eylea vial kit and determined that comparative use human factors study results do not need to be submitted with Celltrion's marketing application seeking licensure as a (b) (4) biosimilar to Eylea for their proposed product CT-P42 vial kit.[f]
- On June 23, 2023, we reviewed the HF validation study protocol submitted for the CT-P42 PFS. During the review of the HF validation study protocol, we noted that in the submission the regulatory pathway being pursued was not immediately clear, i.e., whether the proposed product was a biosimilar to Eylea *versus* an (b) (4) biosimilar to Eylea. As such, On February 14, 2023, we issued an information request (IR) to Celltrion requesting clarification on their planned regulatory pathway for their proposed CT-P42 PFS. In Celltrion's IR response dated February 21, 2023, Celltrion clarified that CT-P42 PFS is a proposed (b) (4) biosimilar to Eylea.[g] Based on this aforementioned information, we determined that HF validation study data is not the appropriate data needed to support (b) (4). The appropriate data to support (b) (4) may be collected from comparative analyses which include comparative task analysis, labeling comparison (including the IFUs), and physical comparison between the proposed CT-P42 PFS and Eylea PFS.

  However, we conducted a high-level review of the HF validation study protocol and found that the protocol required revisions to ensure that adequate data would be collected to support the user interface can be used safely and effectively. We provided HF validation study protocol identified issues and recommendations as well as comments regarding the appropriate data needed to (b) (4) to Celltrion.[h]

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[e] Fashina O. Human Factors Validation Study Protocol Incomplete for CT-P42 (IND 147335). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 JAN 19. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806ab359.

[f] Getahun, S. Use Related Risk Analysis and Comparative Analyses for CT-P42 vial kit (IND 147335). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 MAR 16. TTT No.: 2022-2441.

[g] Response to Information Request (IND 147335 CT-P42). Yeonsu-gu, Incheon (Republic of Korea): Celltrion Inc.; 2023 FEB 21. Available from: \\CDSESUB1\EVSPROD\ind147335\0041\m5\53-clin-stud-rep\535-rep-effic-safety-stud\diabetic-macular-edema\5354-other-stud-rep\ct-p42\response-to-information-request.pdf

[h] Getahun S. Human Factors Validation Study Protocol Review Memo for CT-P42 PFS (IND 147335). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 JUN 23. TTT No.: 2023-3567.

- On June 29, 2023, Celltrion submitted BLA 761377 for CT-P42, which included comparative analyses between their proposed CT-P42 PFS and vial kit to the Eylea PFS and vial kit, which are the subject of this review.

2 MATERIALS REVIEWED

We considered the materials listed in Table 2 for this review. The Appendices provide additional information.

Table 2. Materials Considered for this Review

Material Reviewed	Appendix/Section (for Methods and Results)
Product Information/Prescribing Information	Table 1 (Section 1.1)
Background Information Previous DMEPA HF Reviews and FDA/Sponsor Interactions	A
Human Factors Related Submission Documents	B
Information Requests Issued During the Review	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED

Celltrion submitted URRAs and comparative analyses between their proposed CT-P42 PFS and vial kit products and Eylea PFS and vial kit.

CT-P42 Vial Kit

3.1 USE-RELATED RISK ANALYSES AND COMPARATIVE ANALYSES

We note that the URRA and comparative analyses submitted under BLA 761377 for the proposed CT-P42 vial kit do not differ substantially from the URRA and comparative analyses submitted previously on October 18, 2022, under IND 147335 and that no major differences have been introduced to the vial kit user interface since our review under IND 147335. As such, we maintain our previous recommendation that comparative use human factors study results do not need to be submitted with the marketing application seeking licensure as a (b) (4) biosimilar to Eylea vial kit for the proposed CT-P42 vial kit.

3.2 USE-RELATED RISK ANALYSES

Celltrion submitted a use-related risk analysis (URRA) for their proposed product, CT-P42 PFS.

We reviewed the URRA for the proposed product and based on the information we have at this time, the tasks evaluated appear to be comprehensive and appropriate based on what Celltrion proposes for the design and intended use of this product. Furthermore, for the tasks evaluated in the URRA, we did not identify any additional use-related issues that were not analyzed. Based on Celltrion's identified use-related risks for this product, we determined the risks are mitigated by the proposed labels and labeling.

3.3 COMPARATIVE ANALYSES

The proposed product has the same indications (omitting the additional indication of retinopathy of prematurity for Eylea), intended user populations (qualified physicians), and use environments (controlled aseptic conditions) as the Eylea PFS.

3.3.1 PHYSICAL COMPARISON

Celltrion did not identify any physical difference between the CT-P42 PFS and Eylea PFS as "other" design differences.

Celltrion categorized the following physical difference between the CT-P42 PFS and Eylea PFS as minor:

- Eylea PFS is a 1 mL glass Luer-lock PFS whereas CT-P42 PFS is a 0.5 mL (b) (4) Luer-lock prefilled syringe. Celltrion states, "*Although the material is different, the risk of breakage is low due to the plastic material. In addition, since the break-loose force and gliding force of the CT-P42 PFS is lower than that of Eylea, there is no additional risk from a usability perspective.*"
- CT-P42 PFS has lower break-loose and gliding forces as compared to Elyea PFS.
- CT-P42 PFS plunger rod height (CT-P42 PFS plunger rod height 52.9 ± 0.5 mm vs. 59.9 mm Eylea PFS) and pad diameter (CT-P42 PFS pad diameter 12 mm vs. 19.76 mm Eylea PFS) are smaller than Eylea PFS. Celltrion states, "*The height and diameter of the finger pad of the plunger rod of CT-P42 are smaller than those of US-licensed Eylea, but are larger than in size to the plunger rod of Lucentis, another commercial ophthalmic product. Therefore, plunger rods of a similar size to those of CT-P42 are generally used parts. So there is no additional risk for use.*"

We find the physical differences identified by Celltrion to be minor because they are not likely to impact critical tasks.

We defer the review of the acceptability of the device specifications to the Office of Pharmaceutical Quality (OPQ).

3.3.2 COMPARATIVE TASK ANALYSES

Celltrion did not identify task differences between the proposed CT-P42 PFS and the Eylea PFS. We did not identify any other new, differing, or unique tasks for the proposed CT-P42 PFS as compared to the Eylea PFS.

3.3.3 LABELING COMPARISON

Celltrion did not identify any labeling difference between the CT-P42 PFS and Eylea PFS as "other".

Celltrion categorized the following labeling differences (specifically between the instruction for use (IFU) that is embedded in the prescribing information) between the CT-P42 PFS and Eylea PFS as minor:

- Instructions in the Important Information section in the CT-P42 PFS IFU includes additional instructions to check the drug name and the recommended dose before proceeding with the injection.
- Inclusion of storage information in the CT-P42 PFS IFU whereas this information is only included in section 16 for the Eylea PI.
- Instructions in the prepare for administration section in the CT-P42 PFS IFU includes instructions to gather your supplies whereas Eylea PFS IFU does not.
- Instructions in the administration section in the CT-P42 PFS IFU includes an additional figure to help the user inspect the air bubbles in the syringe.
- Instructions in the administration section in the CT-P42 PFS IFU includes an additional figure to emphasize the accurate positioning of the plunger.
- Regarding removing the needle shield, instructions in the Eylea PFS IFU instruct users to remove the needle shield after step 4 (after attaching the needle) whereas instructions in the CT-P42 PFS IFU instruct users to remove the needle shield after step 9. Celltrion states, "*Based on the HF formative study, intended users usually remove the needle shield after removing air bubbles and dose setting to ensure of the sterility of the needle for as long as possible. Therefore, to avoid confusing, CT-P42 instructs the user to remove the needle shield after Step 8. Remove air bubbles and set the dose. There is no additional risk.*"

We find the labeling differences identified by Celltrion to be minor, and we note that the DMEPA 1 primary review team will evaluate the product specific label and labeling under a separate cover.

4 CONCLUSION

We reviewed Celltrion's use-related risk analyses and comparative analyses between the proposed CT-P42 PFS and vial kit and the Eylea PFS and vial kit and we have concluded that no further information or data (e.g., data from a comparative use human factors study) is needed to support this marketing application. We have no human factors recommendations for this marketing application.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. BACKGROUND INFORMATION

A.1 PREVIOUS REVIEWS RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

A.1.1 Methods

On July 17, 2023, we searched FDA previous reviews using the terms CT-P42, IND 147335, and BLA 761377 to identify reviews previously performed by DMEPA.

A.1.2 Results

Our search identified two previous reviews[i,j] and we considered our previous recommendations to see if they are applicable for this current review.

APPENDIX B. HUMAN FACTORS RELATED SUBMISSION DOCUMENTS

Prefilled Syringe (PFS):

- Comparative Analysis is available in EDR via: \\CDSESUB1\EVSPROD\bla761377\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\diabetic-macular-edema\5354-other-stud-rep\ct-p42\5354-comparative-analysis-for-ctp42-pfs.pdf
- Use-related Risk Analysis (URRA) is available in EDR via: \\CDSESUB1\EVSPROD\bla761377\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\diabetic-macular-edema\5354-other-stud-rep\ct-p42\appendix-1-of-5354-pfs.pdf
- Human Factors (HF) formative study report is available in EDR via: \\CDSESUB1\EVSPROD\bla761377\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\diabetic-macular-edema\5354-other-stud-rep\ct-p42\appendix-2-of-5354-pfs.pdf
- Instructions for Use (IFU) is available in EDR via: \\CDSESUB1\EVSPROD\bla761377\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\diabetic-macular-edema\5354-other-stud-rep\ct-p42\appendix-3-of-5354-pfs.pdf

Vial Kit:

- Comparative Analysis is available in EDR via: \\CDSESUB1\EVSPROD\bla761377\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\diabetic-macular-edema\5354-other-stud-rep\ct-p42\5354-comparative-analysis-for-ctp42-vialkit.pdf

[i] Getahun S. Use-related Risk Analysis and Comparative Analysis Review for CT-P42 (IND 147335). Silver Spring (MD); FDA, CDER, OSE, DMEPA 1 (US); 2023 MAR 16. TTT ID No.: 2022-2441.

[j] Getahun S. Human Factors Validation Study Protocol Review for CT-P42 (IND 147335). Silver Spring (MD); FDA, CDER, OSE, DMEPA 1 (US); 2023 JUN 23. TTT ID No.: 2023-3567.

- URRA is available in EDR via: \\CDSESUB1\EVSPROD\bla761377\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\diabetic-macular-edema\5354-other-stud-rep\ct-p42\appendix-1-of-5354-vialkit.pdf
- HF formative study report is available in EDR via: \\CDSESUB1\EVSPROD\bla761377\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\diabetic-macular-edema\5354-other-stud-rep\ct-p42\appendix-2-of-5354-vialkit.pdf
- IFU is available in EDR via: \\CDSESUB1\EVSPROD\bla761377\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\diabetic-macular-edema\5354-other-stud-rep\ct-p42\appendix-3-of-5354-vialkit.pdf

APPENDIX G. PRODUCT SAMPLE AND LABELS AND LABELING

G.2 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[k] along with postmarket medication error data, we reviewed the following labels and labeling submitted by Celltrion received on June 29, 2023, under the BLA.

- Container Labels
- Carton Labeling
- Prescribing Information (Image not shown) available in the EDR via: \\CDSESUB1\EVSPROD\bla761377\0001\m1\us\annotated-comparison-listed-drug.pdf

[k] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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